REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The specification has been amended to include a Sequence Listing submitted herewith on separate sheets. Entry of the Sequence Listing does not raise the issue of new matter as the sequence information contained therein is presented in the application as originally filed. The computer readable copy of the Sequence Listing submitted herewith is believed to be the same as the attached paper copy of that Listing.

The claims have been revised to define the invention with additional clarity (claim 13 has been revised to indicate that the nucleic acid encodes the antitoxin). Claims 5-9, 11 and 17 have been cancelled without prejudice. The claims as presented find support throughout the application, including in the Examples beginning at page 34. That the claims have been revised should not be taken as an indication that Applicants agree with any view expressed by the Examiner. Rather, the claims have been revised to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

Claims 1-17 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Claims 4 and 7-9 stand further rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejections is in order for the reasons that follow.

The Examiner contends that there is no evidence that the methods claimed in claims 1 and 11 could be used successfully in humans, in particular, for therapeutic purposes. The Examiner further contends that neither the specification nor the art provides any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when the toxins are administered *in vivo* to control cell proliferation.

The claims as now presented relate to use of the ParD kid toxin in combination with its antitoxin, kis, to bring about selective cell cycle inhibition and/or killing in eukaryotic cells.

Applicants have shown for the first time that the ParD kid toxin inhibits cell cycle progression and cell proliferation in yeast and human cells *in vitro* (Examples 1 and 3) and also that this toxin can inhibit cell cycle progression *in vivo* in *Xenopus* embryos (Example 2). Furthermore, Applicants have shown that it is possible to introduce the ParD kid toxin and kis antitoxin into eukaryotic cells *in vitro* and *in vivo* under appropriate control such that kid selectively affects those cells from which kis is absent (Examples 1 to 3).

Submitted herewith is an article by Slanchev et al, which co-authored by one of the inventors named on the subject application. The article shows that the kid toxin can also inhibit cell proliferation and/or cell cycle progression *in vivo* in zebrafish embryos and that kis is innocuous and protects from kid toxicity (see page 4076, left-hand column, paragraphs 2 and 3).

Slanchev et al also demonstrate that kid and kis can be used to selectively kill cells in a whole eukaryotic organism. Slanchev et al cotransformed zebrafish embryos with two types of mRNA construct, containing the kid and kis open reading frames (ORFs), respectively. These embryos developed into sterile adult fish lacking germ cells but with no further somatic defects, indicating that kid had selectively killed the primordial germ cells but had no effect on the somatic cells.

Zebrafish are known to be useful model organisms for use in investigating diseases and treatments of mammals, including humans. Zebrafish have many of the same organs as mammals and most human genes have homologs in zebrafish. Thus, the showing that the ParD kid toxin and kis antitoxin can be introduced into zebrafish under appropriate control to bring about selective killing of cells, along with the *Xenopus in vivo* and the *in vitro* data, is reasonably

predictive that the same is true for mammals, including humans. This is particularly the case as Applicants have shown that the kid toxin can inhibit cell cycle progression and cell proliferation in human cells *in vitro*. This selectivity in cell killing helps to overcome the alleged problems of toxicity to normal cells and immunogenicity of the toxin suggested by the Examiner to be a barrier to therapeutic use of toxins.

To summarize, the kid toxin inhibits cell cycle progression and cell proliferation both *in vitro* and *in vivo* in a variety of eukaryotic cells, including human cells, and can be introduced into eukaryotic cells *in vivo* under appropriate control for selective cell cycle inhibition and/or killing. Such selectivity in cell killing can be brought about in zebrafish, known to be a good model for human diseases and treatments.

Thus, the kid toxin can be used to inhibit *in vitro* and *in vivo* cell proliferation and/or cell cycle progression in other eukaryotes, such as humans. In particular, it can be used in combination with its antitoxin, kis, to bring about *in vitro* and *in vivo* selective cell cycle inhibition and/or killing in other eukaryotes, including humans. Indeed, the Examiner acknowledges that claims to such methods using the ParD kid toxin (e.g., previous claim 9) are enabled.

The Examiner also contends that claims wherein the toxin targets DnaB (previous claims 7 to 9) are not enabled. All such claims have been deleted thereby rendering moot the rejection thereof as lacking enablement.

In view of the above, reconsideration is requested.

Claims 1-17 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and comments that follow.

Claim 1 has been amended to more clearly indicate that the methods are for inhibiting cell proliferation in eukaryotic cells. Claim 11 has been cancelled.

The Examiner contends that the term "target cells" in claim 1 lacks antecedent basis and thus is unclear. The above-noted revision of claim 1 is believed to address the Examiner's concerns.

The Examiner also contends that the phrase "an inhibitor of said toxin, optionally an antidote to the toxin wherein both toxin and antidote are proteins, under appropriate control for selective cell cycle inhibition" is unclear. Claim 1 has been amended to make it clear that the "appropriate control" is not optional and that both the toxin and the antitoxin are under appropriate control. Further, the claims no longer refer to an "antidote" or "inhibitor".

The phrase "A method of inhibiting cell proliferation and/or cell cycle progression" in claim 1, to which the Examiner objects, has been deleted.

As suggested by the Examiner, all of the dependent claims now begin with "The" rather than "A".

The Examiner contends that, in claim 12, it is unclear whether "controlling activity of said antidote" is meant to be an active step or a further limitation of the "appropriate control" in claim 1. Claim 12 has been amended in a manner that is believed to address the Examiner's concern.

The Examiner also alleges that there is no basis in the application for controlling the activity of the antidote, only controlling the presence and amount of the antidote. Thus the Examiner contends that the reference to "controlling activity" of the antidote, as used in claim 12, lacks antecedent basis. While Applicants are uncertain as to the basis for the Examiner's concern, they direct attention to the fact that basis for controlling activity of the antidote is found

in the application on page 15, lines 8 to 10. Furthermore, it is clear from elsewhere in the specification (e.g., page 15, lines 1; page 5, lines 9 to 11 and page 16, lines 25 to 27) that 'controlling production' is a sub-set of 'controlling activity'. Thus, if, as acknowledged by the Examiner, there is basis in the application for controlling production of the antidote (in this case ParD kis antitoxin), there is basis for controlling activity of the antidote. Additionally, methods for controlling the activity of a protein (e.g., a toxin antidote such as the ParD kis antitoxin) are well known in the art. For example, methods to promote the degradation of particular proteins are known.

In view of the above, reconsideration is requested.

Claims 1-6, 10 and 11 sand rejected under 35 USC 102(b) as allegedly being anticipated by Molin et al. Claims 1, 2, 6, 8, 10 and 12-16 stand rejected under 35 USC 102(b) as allegedly being anticipated by Paulus et al. Withdrawal of these rejections is in order for the reasons that follow.

All of the claims as amended refer to the use of the ParD kid toxin and kis antitoxin. Neither Molin et al or Paulus et al mentions the ParD kid toxin or kis antitoxin. Therefore, all the claims as now presented are novel over both Molin et al and Paulus et al. Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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